

Synthesis and Properties of a New Type of Unsaturated Poly(ester amide)

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ABSTRACT: A new type of unsaturated poly(ester amide), maleic anhydride–phthalic anhydride–ethylene glycol–neopentylene glycol–anthranilic acid copolymer, was prepared by melt polycondensation. The copolymer was characterized by Fourier transform infrared spectroscopy, gel permeation chromatography, and thermogravimetric analysis. The viscosity of the polymer was measured with a Ubbelohde viscometer. The compressive strength of the crosslinked unsaturated poly(ester amide) under different heat-treatment conditions was measured. Studies of its degradation behavior were carried out in simulated body

fluid at pH 7.4 (37°C), and the compressive strength loss of the crosslinked unsaturated poly(ester amide) was also measured after different degradation times. The copolymer was hydrolyzed in a 1.0-mol/L NaOH standard solution at room temperature. All of the preliminary results suggest that the new unsaturated poly(ester amide) might potentially be used as a new type of bone-fixation material. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 1208–1212, 2009

Key words: biological applications of polymers; biomaterials; biopolymers; degradation

INTRODUCTION

Orthopedic, craniofacial, and oral–maxillofacial surgeons often use tissue-fixation devices, such as pins, plates, and screws that are made out of poly(L-lactic acid).^{1–3} Although biodegradable devices have significant advantages over their metal counterparts, there are also some concerns with their use. These concerns include bulk degradation behavior and their inability to fully strengthen with bone. To overcome the problems associated with the bulk degradation of widely used polyester orthopedic devices [e.g., poly(L-lactic acid), poly(glycolic acid), and their copolymers],^{4,5} crosslinking polyanhydrides have been developed in the past several years.⁶ In contrast with polyesters, polyanhydrides undergo a surface-eroding degradable mechanism, which effectively maintains the mechanical integrity and strength by preserving the molecular weight of the polymer, and the polymers exhibit a gradual loss in size that permits bone to grow little by little.⁷ In addition, crosslinked polyanhydrides can be easily fabricated into desirable shapes; therefore, they demonstrate a great potential for bone-fixation applications and might be a better alternative than

polyesters as internal fixation materials.^{8,9} However, the mechanical strength, especially the compressive strength, of these reported materials are still far lower than that of cortical bones and needs to be further increased to meet the need of load-bearing bones during rehabilitation.

Degradable ester groups and high polarity N–H bonds are included in poly(ester amide), which gives the polymer good mechanical properties. However, a reported unsaturated poly(ester amide) had low mechanical properties after crosslinking and could be easily degraded.¹⁰ Compared to unsaturated poly(ester amide), saturated poly(ester amide) is a type of elastomer that has lower mechanical properties and a higher degradation rate.^{11–16} At the same time, all of the reported poly(ester amide)s have had very complex reaction conditions, and amide bonds were included by the addition of an amino acid as a raw material mostly.^{17–28} In this study, a new type of unsaturated poly(ester amide), maleic anhydride–phthalic anhydride–ethylene glycol–neopentylene glycol–anthranilic acid copolymer, was prepared by melt polycondensation, and the ends were sealed with benzyl alcohol to improve its water-resistance performance during degradation in simulated body fluid (SBF). Product characterizations were investigated with polymers containing different ethylene glycol (EG)/neopentylene glycol (NG) ratios before and after crosslinking with vinyl acetate as the crosslinker. The mechanical and degradation properties were also recorded after heat treatment.

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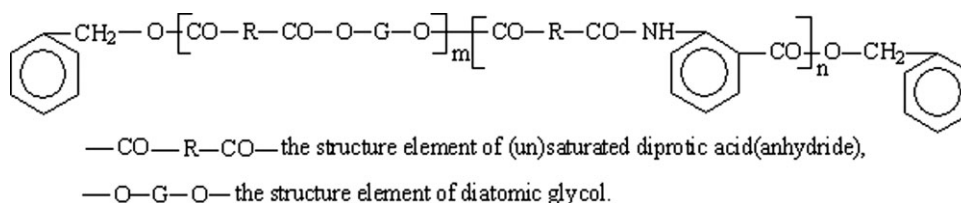


Figure 1 Structural formula of the synthesized unsaturated poly(ester amide).

EXPERIMENTAL

Materials

Phthalic anhydride (purity $\geq 98\%$), maleic anhydride (purity $\geq 95\%$), and anthranillic acid (purity = 98%) were purchased from Tianjing Central Pharmaceutical Corp., Ltd. (Tianjing, China). Ethylene glycol (purity $\geq 99\%$), benzyl alcohol (purity $\geq 98\%$), neopentylene glycol (purity $\geq 99.5\%$), and vinyl acetate (purity $\geq 97.9\%$) were purchased from Zibo Guangtong Chemical Co., Ltd. (Zibo, China).

Unsaturated poly(ester amide) synthesis

In a typical reaction in this study, 0.0225 mol (3.33 g) of phthalic anhydride, 0.04 mol (2.48 g) of ethylene glycol, and 0.055 mol (5.72 g) of neopentylene glycol were added to a flask with two side arms, electrodynamic stirring, and an oil/water separator and polymerized at 160°C for 1 h. Then, we added 0.0775 mol (7.595 g) of maleic anhydride and 0.0125 mol (1.7125 g) of anthranillic acid and raised the reaction temperature to 180°C. The flask was kept still for 1.5 h, and the mixture was polymerized at 195°C for 4 h under a flow of argon. Then, we added 10 wt % benzyl alcohol when the system was cooled to 120°C; we allowed the mixture to react for 1 h, then raised the temperature to 165°C for another 1 h, and raised the temperature to 180°C for another 1 h. After the temperature was decreased to 100°C, the synthesized unsaturated poly(ester amide) samples were moved to a P₂O₅ desiccator. The structural formula of the synthesized unsaturated poly(ester amide) is shown in Figure 1.

Crosslinking

After 0.06 g of benzoyl peroxide was dissolved in 2 g of vinyl acetate, we added 8 g of the synthesized unsaturated poly(ester amide) to the vinyl acetate containing benzoyl peroxide until the vinyl acetate fully dissolved in the copolymer. The mixture was poured into a mold for crosslinking after the addition of 0.03 g of ascorbic acid. After 18 h, the crosslinked samples were placed in an oven at 195°C for 28 h for heat treatment, and the samples were stored in a P₂O₅ desiccator.

Unsaturated poly(ester amide) characterization methods

IR spectra were obtained with a Bruker EQUINOX55 Fourier transform infrared spectrometer (Beijing, China). The synthesized unsaturated poly(ester amide) samples were put directly onto NaCl plates to record the IR spectra. The viscosity of the polymers was measured with an Ubbelohde viscometer (Changsha, China), and the molecular weights of the synthesized unsaturated poly(ester amide)s were determined on a Waters gel permeation chromatography system (Shanghai, China) consisting of a Waters 600 pump and a Waters 410 differential refractive index detector. Samples were eluted in dichloromethane through Varian Micropak G4000 and G3000 columns installed (Shanghai, China) in series at a flow rate of 1.0 mL/min. The molecular weights were determined relative to narrow dispersed polystyrene standards with a molecular weight range from 1000 to 200,000. Thermal analyses were performed on a PerkinElmer system consisting of DSC 7 and TGA 7 analyzers (Wuhan, China) with a TAC7/DX instrument controller. Data were processed with Unix thermal analysis system software on a DEC computer station (Wuhan, China). For thermogravimetric analysis (TGA), samples with an average weight of 10 mg were heated at 10°C/min under a flow of argon. The decomposition temperature was detected by TGA.

Degradation methods

In vitro, the degradation of rectangular samples (5 × 5 × 45 mm³) in 50 mL of 0.1-mol/L phosphate buffer solution (pH 7.4) were performed in an incubator shaker (model HQ45A, Factory of Scientific Instrument, Wuhan, China) agitated at 60 rpm with a constant temperature of 37 ± 1°C in an air bath. The phosphate buffer solutions were changed daily, and the rectangular (5 × 5 × 45 mm³) crosslinked unsaturated poly(ester amide) samples were carefully freeze-dried before their mechanical strengths were measured after some time of degradation. The rectangular samples (5 × 5 × 45 mm³) were also hydrolyzed in a 1.0-mol/L NaOH standard solution at room temperature. The cumulative mass loss was measured after different hydrolysis times. All measurements were carried out in triplicate with three separate devices.

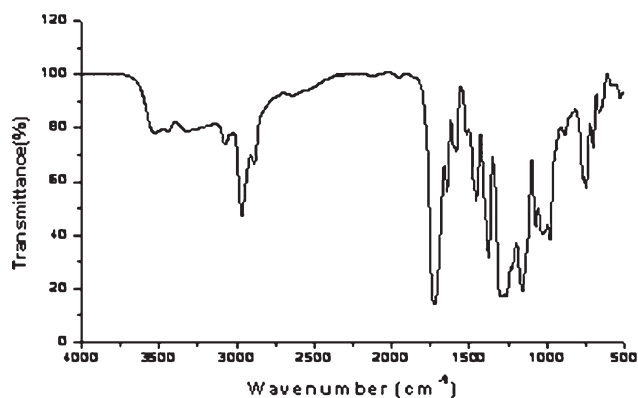


Figure 2 IR spectrum of the synthesized unsaturated poly(ester amide).

All the detected data were processed with Microcal Origin 6.1 software on a personal computer.

RESULTS AND DISCUSSION

Synthesized unsaturated poly(ester amide) characterization

The IR spectrum of the synthesized unsaturated poly(ester amide) shown in Figure 2 showed strong absorption peaks at $1710\text{--}1735\text{ cm}^{-1}$, which were characteristic absorptions of the carbonyl stretching vibrations of ester groups, which occurred in the IR spectra of all of the products. The absorption bands at 2966 and 2887 cm^{-1} were characteristic of the C—H stretching vibrations of aliphatic alkyl groups; those at 1645 cm^{-1} were attributed to C=C stretching vibrations, and those at $1225\text{--}1157\text{ cm}^{-1}$ were attributed to the C—O stretching of the ester group. The absorption peak of N—H appeared at about 3442 cm^{-1} and the absorption peak of the C—N stretching of the amide group appeared at about 1296 cm^{-1} on the Fourier transform infrared spectra.

TABLE I
Physical Properties of the Synthesized Unsaturated Poly(ester amide)

Mol number of ethylene glycol (M_{EG}) : Mol number of neopentylene glycol (M_{NG})	Viscosity (dL/g) ^a	Molecular weight ^b	
		Weight-average molecular weight (M_w)	Number-average molecular weight (M_n)
2 : 1	0.70	3510	3098
1 : 1	0.71	3610	3190
1 : 2	0.73	3822	3423

^a Inherent viscosity determined in chloroform with an Ubbelohde viscometer at 23°C before crosslinking.

^b Before crosslinking.

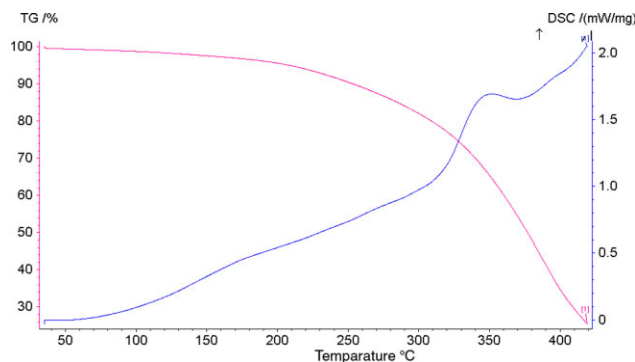


Figure 3 Differential scanning calorimetry–thermogravimetry figure of the synthesized unsaturated poly(ester amide). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

As shown in Table I, the weight-average molecular weights of the prepared copolymers were between 3000 and 5000. As the neopentylene glycol content was raised, the viscosity and molecular weight of the synthesized unsaturated poly(ester amide) also increased. The viscosity was over 0.7, which showed that the low polymer was a high-viscosity copolymer, but as the temperature was raised, the viscosity decreased very quickly. When the temperature was over 80°C , the low polymer had good fluidity. The value of the decomposition temperature as determined by TGA was over 200°C for the copolymer, which suggested that the copolymer possessed a desired thermal stability for heat treatment (Fig. 3).

Compressive strength of the crosslinked unsaturated poly(ester amide) with different heat-treatment conditions

The compressive strength of the crosslinked unsaturated poly(ester amide) is shown in Figure 4. As shown in Figure 4, when the heat-treatment

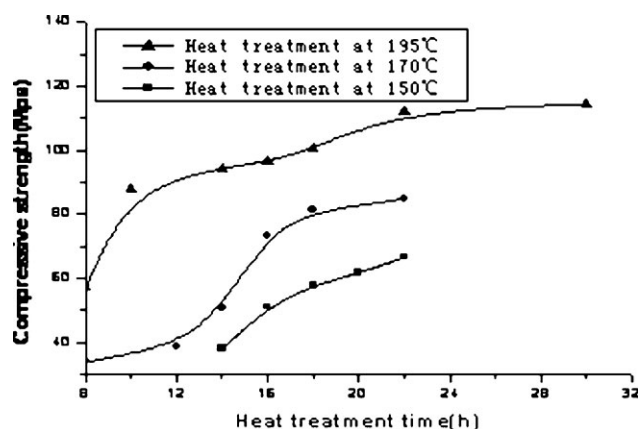


Figure 4 Compressive strength changes of the crosslinked unsaturated poly(ester amide) with different heat-treatment temperatures and a 20 wt % crosslinker content.

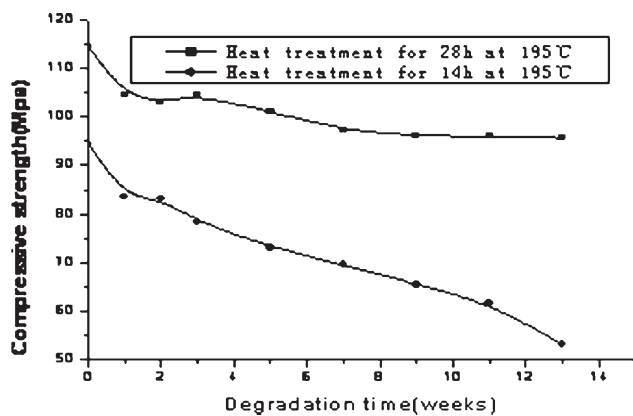


Figure 5 Compressive strength loss of the crosslinked unsaturated poly(ester amide) containing 20% crosslinker in SBF at pH 7.4 and 37°C after heat treatment at 195°C.

temperature or time was increased, the compressive strength improved step by step. Furthermore, the increments of the compressive strength when the heat-treatment time was increased from 8 to 16 h were much higher than those when heat-treatment time was increased from 16 to 28 h. Moreover, the compressive strength of the crosslinked unsaturated poly(ester amide) with heat treatment for 28 h at 195°C was about two times the corresponding compressive strength of the crosslinked unsaturated poly(ester amide) with heat treatment for 8 h (Fig. 4). When the heat-treatment temperature was over 210°C, the unsaturated poly(ester amide) decomposed. In addition, our studies showed that the heat-treatment time played an especially crucial role in increasing the compressive strength, which is very important for biomaterials. In addition, when the heat-treatment time and heat-treatment temperature were increased, the degradation properties showed better results, which might have been because of the longer heat-treatment time because the molecules had a higher degree of crosslinking; thus, the molecular structure was closer. When the crosslinked unsaturated poly(ester amide) degraded, the outside liquid could not easily be invaded, which decreased the crosslinked unsaturated poly(ester amide) degradation speed. All of the research indicated that it had good compressive strength to meet the essential requirements for bone-fixation materials when it was heat-treated at 195°C for 28 h and contained 20 wt % crosslinker.

Degradation behavior of the unsaturated poly(ester amide)

The compressive strength loss of the crosslinked unsaturated poly(ester amide) in SBF at pH 7.4 and 37°C is shown in Figure 5. As shown in Figure 5, the compressive strength of the crosslinked unsaturated poly(ester amide) dropped as the degradation time was raised. A longer heat-treatment time caused a lower compressive strength loss rate because, when the heat-treatment time was raised, the degree of crosslinking of the copolymer also increased, which decreased the compressive strength loss rate. During the first 3 weeks, the compressive strength of the crosslinked unsaturated poly(ester amide) containing 20 wt % crosslinker dropped 17.0% when it was heat-treated for 14 h and 9.6% when it was heat-treated for 28 h. After 3 months of degradation in SBF at pH 7.4 and 37°C, the compressive strength of the crosslinked unsaturated poly(ester amide) heat-treated for 28 h remained at 95.7 MPa. Therefore, it would be possible to prepare the copolymer material as a new type of cancellous bone (compressive strength = 5–20 MPa) fixation device through the recombination of material or adjustment of the chemical composite in the crosslinking copolymer network to meet the need of cortical bone (compressive strength = 110–167 MPa).

Hydrolysis behavior of the crosslinked unsaturated poly(ester amide)

In vitro, the degradation properties of the crosslinked unsaturated poly(ester amide) were studied in SBF at pH 7.4 and 37°C, and the results show that the mass of the polymer lost about 0.4% after 3 months of degradation. The hydrolysis behavior of the copolymer after heat treatment at 195°C with different heat-treatment times or crosslinker contents was determined by quantitative analysis of the mass loss in a 1.0-mol/L NaOH standard solution at room temperature. The results are shown in Table II. It was clearly demonstrated that the hydrolysis rate of the crosslinked unsaturated poly(ester amide) was related to the heat-treatment conditions and crosslinker content. When the heat-treatment time was over 14 h at 195°C, the crosslinked unsaturated poly(ester amide) had already crosslinked completely; at the same time, the hydrolysis rate of the

TABLE II
Mass Loss Rate of the Crosslinked Unsaturated Poly(ester amide) in a 1.0-mol/L NaOH Standard Solution at Room Temperature with Different Heat-Treatment Times at 195°C and Crosslinker Contents

Heat-treatment time (h)	14	18	22	28	14	14	14
Crosslinker content (wt %)	20	20	20	20	30	40	50
Mass loss (%) after 5 days of hydrolysis	17.14	12.71	13.88	14.01	19.44	32.9	67.78
Mass loss (%) after 15 days of hydrolysis	24.28	19.64	19.44	19.32	30.51	62.58	90.74
Mass loss (%) after 25 days of hydrolysis	29.04	26.78	27.77	27.43	40.20	85.81	98.12

crosslinked unsaturated poly(ester amide) containing 20 wt % crosslinker almost did not change.

During the tested periods, the dimensions of the devices decreased step by step with mass loss, and the surface of the devices remained slick during the hydrolysis process. It showed surface erosion properties. After about 30 days of hydrolysis, the dimensions of the crosslinked unsaturated poly(ester amide) that contained 20 wt % crosslinker and was heat-treated at 195°C for 28 h decreased by about half, and then, it gradually vanished.

CONCLUSIONS

An unsaturated poly(ester amide) with desired physicochemical properties was successfully prepared by melt polycondensation, and with an increase in neopentylene glycol content, the viscosity and molecular weight of the unsaturated poly(ester amide) also increased a little. All of the prepared copolymers possessed the desired thermal stability. After heat treatment under different conditions, the heat-treatment time or temperature dramatically increased the compressive strength and the maximum compressive strength of the crosslinked unsaturated poly(ester amide), which was about 114.5 MPa. After degradation for 3 months in SBF at pH 7.4 and 37°C, the compressive strength of the crosslinked unsaturated poly(ester amide) remained at 95.7 MPa when it was heat-treated for 28 h at 195°C and contained 20 wt % crosslinker. The heat-treatment conditions and crosslinker content played important roles in holding the mass loss rate during the hydrolysis process in a 1.0-mol/L NaOH standard solution at room temperature, and during the tested periods, it showed surface erosion properties. All of the preliminary results suggest that the new unsaturated poly(ester amide) might potentially be used as a new type of bone-fixation material.

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